CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

63065

BIOEQUIVALENCY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA: 63-065 DRUG PRODUCT: Minocycline Hydrochloride

FIRM: Danbury Pharm. DOSAGE FORM: Capsules STRENGTH: 100mg

CGMP STATEMENT/EIR UPDATE STATUS: EER update requested 11/14/91. **Acceptable EER granted 11/25/91** per Bob Pollock. Firm needed to delete as an alternate facility for micro testing due to CGMP problems. Dave Doleski contacted firm to verify. was withdrawn in a telephone amendment dated November 22,1991 and faxed to OGD (copy attached).

BIO INFORMATION: Firm utilizes methodology recommended by Division of Bio for comparative dissolution. **Waiver granted 8/22/91 for 50mg capsules.** Firm conducted a bio study for 100mg capsules using material from only approved NDS supplier (see bio batch section below).

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Antimicrobial Drugs Branch tested 3 batches of the product as follows; #00755C manufactured on 8/16/88- capsules
#01218C manufactured on 1/10/89- capsules
#01219C manufactured on 1/10/89- capsules
Analytical results satisfactory-meets compendial requirements. At time of testing validation, maximum batch size was in question. However, this has been resolved due to firm's commitment to produce a batch no larger than until such time as data for a larger batch size is submitted and approved. Stability issues have been adequately addressed (see below).

STABILITY-ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE USED IN THE CONTAINER SECTION? Above batches listed in Validation section were placed on stability at controlled room temp for up to 7 months as well as accelerated conditions (40 oC/75%RH for 3 mos. Batch # 00755C was manufactured using bulk NDS, an un approved supplier. When firm withdrew they placed an additional batch, # 02300C-31,741 capsules, on stability (above conditions) and , **therefore, all three batches were from the approved NDS supplier** Stability data was generated on smallest (50's) and largest (500's) container sizes. The container/closure system is the same as listed in the container section.

LABELING- Satisfactory per J. Phillips on 11/13/91.

STERILIZATION VALIDATION (IF APPLICABLE)- NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?)- Originally firm requested two suppliers of bulk NDS,
was approved May 31, 1990 but was not approved.
was withdrawn as a supplier of bulk and a third batch was

manufactured from bulk with supporting data submitted. **An acceptable <u>in vivo</u> bio study was conducted comparing the Danbury 100mg capsules with 100mg capsules of Minocin manufactured by Lederle.** A bio waiver for the 50mg capsules was granted on 8/28/91

SIZE OF STABILITY BATCHES-(IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED USING THE SAME PROCESS AND COMPARABLE EQUIPMENT?)-

The stability and bio batches were the same (see discussion above). Danbury indicated in a letter dated April 10, 1991 (see ANDA Vol 3.1) the batch used for the 100mg capsules was a production sized batch (theoretical yield= actual yield= capsules) **produced with "typical" production equipment.** The facility utilized for manufacture of this batch is the production facility.

PROPOSED PRODUCTION BATCH- MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?-

* See above- The **production batch was produced "in exactly the same manner as all batches previously submitted"**(Danbury letter dated April 10,1991, ANDA-Vol 3.1). The "batches previously submitted" refer to the stability and bio batches discussed above.

RECOMMENDATION: **Approve** based upon satisfactory EER and completion of all aspects of Chemistry and bio review.

SIGNATURE: /S/ DATE: 11/25/91

Minocycline Hydrochloride
100 mg Capsules
ANDA # 63-065
Reviewer: Man M. Kochhar
A:63065BIO

Danbury Pharmacal, Inc.
Danbury, Connecticut
Submission Date:
April ~~10~~ 5, 1991

Review of Bioequivalence Study
and Dissolution Data

8/22/91

Objective:

A two-way, single dose crossover study was performed to determine the bioequivalency of two minocycline hydrochloride formulations. Danbury's 100 mg capsules were compared to 100 mg Minocin^{R} (reference), marketed by Lederle Laboratories.

Introduction:

The sponsor had submitted an approvable bioequivalence study (ANDA # 63-065 dated October 6, 1988). The company has changed the supply source of minocycline hydrochloride and therefore, they have conducted another bioequivalent study on the material obtained from a new source.

Minocycline hydrochloride is a semisynthetic derivative of tetracycline. The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Minocycline hydrochloride is a tetracycline with antibacterial activity comparable to other tetracyclines with activity against a wide range of gram-positive and gram-negative organisms.

Minocycline is well absorbed orally. Peak concentrations occur within 2-3 hours and in the range of mcg/ml with a single 200 mg dose. The serum half-life ranges from 15-23 hours.

About 11% of the dose is excreted unchanged in the urine and 20 to 34% in the feces. The drug is partly metabolized to inactive compounds in the liver.

Study Protocol:

The study was conducted by
under the supervision of

The study employed 26 healthy male volunteers between 18 and 45 years of age whose weight did not deviate by more than ± 15% of the ideal for their height and age (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematologic or renal

disease were employed. In addition, subjects were required to be without history of alcohol or drug abuse and prior sensitivity to the drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, and urinalysis). Subjects were required to take no prescribed medications and OTC products (especially aspirin-containing products) for at least 7 days prior to the initial dosing and to refrain from consumption of alcoholic or caffeine-containing foods and beverages from 24 hours prior to dosing in each period and throughout the time samples were collected in each period.

The subjects were housed in the live-in facility from 12 hours before until 48 hours after drug administration. The subjects fasted for 10 hours prior to the first drug administration of phase 1. No meals were served within 4 hours of any dose. Water ad lib was allowed except within 2 hours of drug administration.

The product and dosage employed in this study were as follows:

A. Test: 1 x 100 mg minocycline capsule, lot # 04308C, with 240 ml of water.
Batch size: capsules

B. Reference: 1 x 100 mg Lederle's Minocin^{R} (minocycline), lot # 268-494 with 240 ml water.

Five (5) ml of venous blood were drawn in Vacutainers with EDTA as an anticoagulant at : 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours. The plasma was separated and promptly frozen for analysis.

Analytical Methodology:

Data Analysis:

Three-way analyses of variance with subject, period and drug formulation as factors, and sequence as a between-subjects factor, were applied to the minocycline pharmacokinetic parameters and to the plasma minocycline concentrations at each sampling point. The Analysis of Variance included calculations of least squares means and estimated differences between the two formulations. Evaluations of bioequivalency were based upon interproduct comparison of AUC, C_{MAX}, T_{MAX}, K_{el} and the timed serum minocycline concentrations.

In-Vivo Bioequivalency Results:

Twenty-six (26) subjects completed the study. The results of the study comparing the bioavailability of minocycline hydrochloride test and reference product are given in Table 1 and 2 and Figure 1.

Table 1

Mean Serum Concentration of Minocycline Hydrochloride with CV% in Parenthesis (N=26)

Time (hours)	Danbury's Minocycline lot # 04308C ng/mL	Lederle's Minocin lot # 268-494 ng/mL
0.5	361.2 (62.7)	247.7 (67.7)
1	705.9 (28.9)	532.4 (37.9)
1.5	748.1 (19.7)	644.5 (28.4)
2	752.2 (13.8)	649.6 (27.1)
2.5	726.2 (15.5)	635.4 (24.3)
3	713.6 (18.8)	646.2 (25.7)
4	669.9 (16.3)	598.1 (21.8)
6	523.9 (16.1)	474.5 (23.3)
8	450.3 (12.8)	395.8 (24.6)
12	371.3 (16.0)	336.0 (27.8)
16	293.7 (18.5)	259.9 (27.6)
24	232.5 (24.2)	201.1 (33.7)
36	127.7 (31.4)	117.0 (36.0)
48	82.6 (44.6)	74.8 (47.4)
72	20.3 (158.3)	27.8 (116.5)

Table 2

A Summary of Pharmacokinetic Parameters for 26 Subjects (CV%)

parameter	Danbury's Minocycline	Lederle's Minocin	% Diff	90%confidence Interval
AUC_{0-72} (ng.hr/mL)	13908.6 (22.5)	12513.0 (31.3)	11.1	102; 120
AUC_{inf} (ng.hr/mL)	15425.7 (24.4)	14102.9 (31.1)	9.4	101; 117
C_{MAX} (ng/mL)	830.7 (15.9)	725.4 (23.3)	14.5	106; 123
T_{MAX} (hours)	1.9 (41.3)	2.0 (42.7)	5.0	
K_{el} (1/hr)	0.044 (20.2)	0.040 (17.0)	10.0	
$t_{1/2}$ (hours)	15.7	17.3	9.0	

The minocycline AUC_{0-72} of the Danbury product was 11% higher than the corresponding Lederle product. The AUC_{inf} was 9% higher than the reference. None of the differences was statistically significant at the 0.05 alpha level. The confidence intervals were well within the $\pm$ 20% limits set for defining product bioequivalence.

The differences between Danbury minocycline hydrochloride and Minocin C_{MAX} was 14.5%. The 90% confidence interval for C_{MAX} was 106 to 123.

The minocycline hydrochloride/time profiles of the two products were similar with less than 20% difference between the products being observed at each of the timed collection points.

No serious adverse events were experienced by any subject during the study.

On the basis of the in-vivo bioavailability data, it is determined that Danbury's Minocycline hydrochloride, 100 mg capsules and Lederle's Minocin^R, 100 mg capsules are bioequivalent.

Dissolution Test Results:

In-Vitro dissolution testing was conducted in apparatus 2 (paddle) at 50 rpm. Results are presented in Table 3. Both the test and

reference products meet the dissolution specification of NLT % of the labeled amount of the drug dissolved from the capsule in 45 minutes.

The lot of test and reference product employed in the in-vitro dissolution tests were identical to those employed in the in-vivo bioequivalence study.

Comments:

1. The study was conducted in 26 normal male volunteers, comparing the plasma concentration from Danbury's Minocycline HCl, 100 mg capsules to that of Minocin^R, 100 mg capsules. The minocycline hydrochloride AUC_{0-72}, AUC_{inf} and C_{MAX} of the Danbury's formulation were 11% higher, 9% higher and 14.5% higher than the corresponding Lederle's reference values. The differences was statistically significant in the case of C_{max}.

2. Under the conditions of this study, the Danbury capsule shows a greater extent of absorption than the Lederle's Minocin. The higher mean C_{max} exhibited by the Danbury capsule most likely reflects a difference between the two formulations in extent, rather than rate of absorption, since the mean T_{max} values are comparable.

3. The comparison of the mean concentrations at each sampling time (Table 1), also indicate that extent of minocycline absorption is greater for the Danbury capsule than the Minocin. Examination of the individual subject data indicated that several subjects exhibited significantly higher Cmax and AUC with Danbury than the reference but did not observe any subjects who were obvious outliers. Part of the difference may be due to lower dose (100 mg) used in this study. The content uniformity for the test product was (102%) compared to the reference Minocin (100.7%). This difference should not effect the C_{max} values.

4. The in-vivo bioequivalence study is acceptable. The firm should be informed accordingly.

5. The in-vitro dissolution testing conducted by the firm is acceptable. Both the test and reference products show greater than % of the labeled amount of minocycline hydrochloride dissolved in 45 minutes.

6. The lots of the test and reference product employed in the in-vitro dissolution test were identical to those employed in the in-vivo bioequivalence study.

Recommendations:

1. The bioequivalence study conducted by Danbury Pharmacal, Inc. on its minocycline hydrochloride, 100 mg capsules, lot # 04308C, comparing it to Minocin^R, 100 mg capsules, lot # 268-494, manufactured by Lederle has been found acceptable by the

Division of Bioequivalence. The study demonstrates that Danbury's minocycline hydrochloride, 100 mg capsules are bioequivalent to reference product, Minocin®, 100 mg capsules manufactured by Lederle Laboratories.

2. The in-vitro test results were also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXII apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than % of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

3. From the bioequivalence point of view, the firm has met the requirements for in-vivo and in-vitro dissolution test and the application is approvable.

The firm should be informed of the recommendations.

/S/

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/

Concur: /S/ Date: 8/16/91.

Shrikant V. Dighe, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/05-30-91/A:63065

cc: ANDA # 63-065 original, HFD-230, HFD-200 (Hare), HFD-340 (Turner), HFD-22 (Hooton), HFD-258 (Mhatre, Kochhar), Drug File

TABLE 4

FORMULATION

Ingredients	Quantity per capsule
Minocycline HCl, USP	mg
Starch, NF, Purity	mg
Magnesium Stearate, NF	mg

Drug (Generic Name): Minocycline HCl
Dose Strength: _____
ANDA # _____

Firm: Danbury Pharmacal
Submission Date: April 10, 1991

Table 3 - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket ___ Paddle ✓ RPM 50 No. Units Tested: 12

Medium: water Volume: 900 ml

Reference Drug; (Manuf.): Lederle

Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.) ~~(Hr.)~~	Test Product Lot # 04308C Strength (mg) 100 Mean % Dissolved	Range	RSD (CV) %	Reference Product Lot # 268-494 Strength (mg) 100 Mean % Dissolved	Range	RSD (CV) %
15	55.9		(35.8)	38.5		(10.8)
30	93.5		(7.3)	62.0		(9.4)
45	98.6		(4.9)	78.7		(7.0)
60	100.5		(4.1)	90.2		(5.5)
			( )			( )

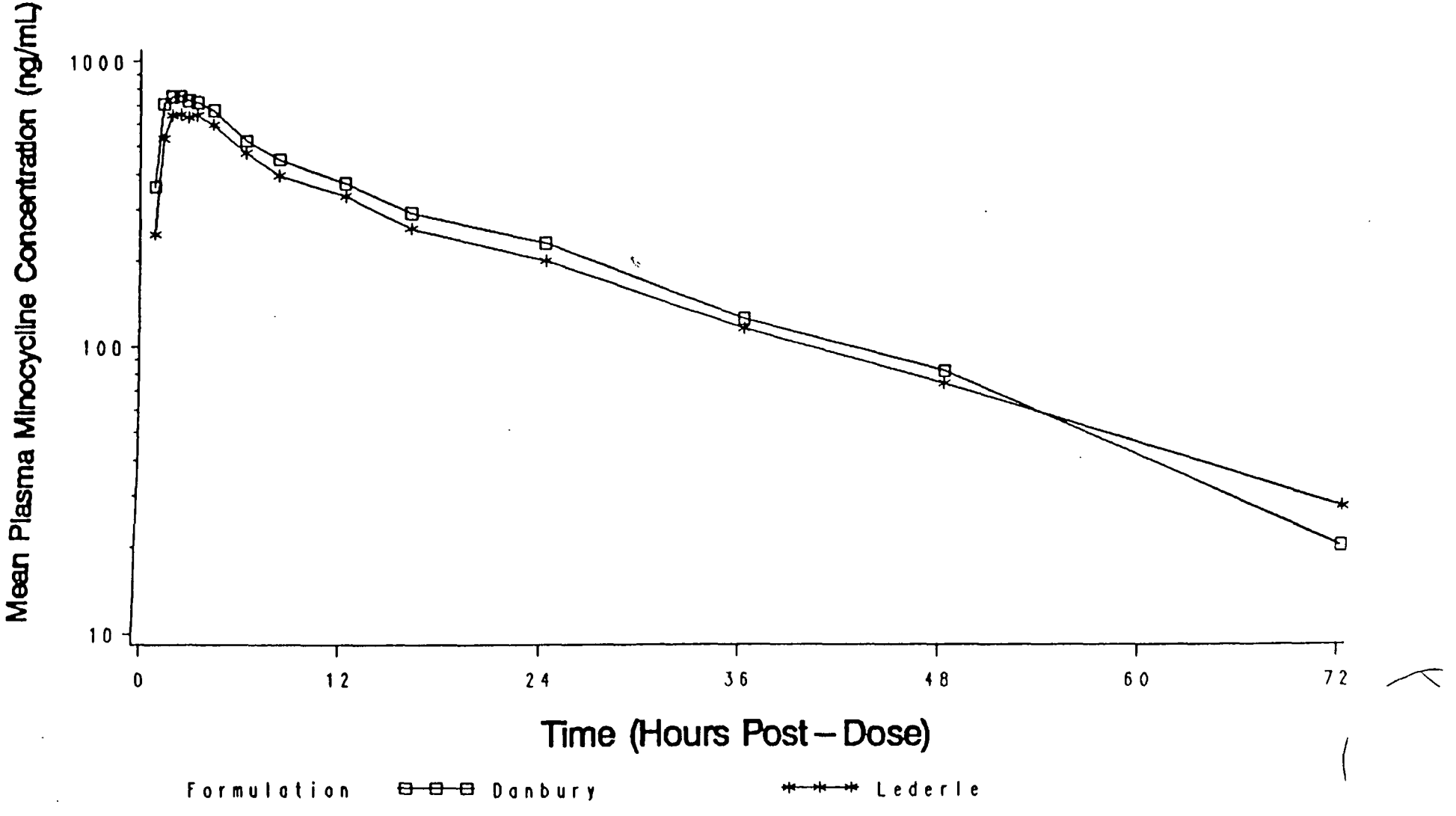
	Lot # _____ Strength (mg) _____			Lot # _____ Strength (mg) _____		
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

Figure 1

Project No. 900780

Mean Plasma Minocycline Concentrations

(Semi – log Plot)



DIVISION OF BIOEQUIVALENCE
IN VIVO STUDY DATABASE
DATA ENTRY FORM

(FOR OFFICE USE ONLY)

SHEET NO. 1

PARAMETERS DERIVED FROM BLOOD/PLASMA DATA — PARAMETERS BASED ON NATURAL LOG TRANSFORMATION OF DATA

DERIVED FROM URINE DATA

ANDA NO.: 63065	PARAMETER	1 AUC	2 AUC(INF)	3 Cmax	4 Tmax	5 AUC	6 AUC(INF)	7 Cmax	8 Kel	9 T1/2	10 CUM	11 ER MAX	12 TER MAX	13	14	15
SUBMISSION DATE: 4/10/91	UNITS	ng·hr/ml	ng·hr/ml	ng/ml	hour											
	HOUR, first TIME POINT															
Danbury Pharmacal	HOUR, last TIME POINT															
SPONSOR																
Minocycline HCl	TEST MEAN	13908.6	15425.7	830.7	1.9											
TEST DRUG NAME	REFERENCE MEAN	12513.	14102.9	725.4	2.0											
Capsule	TEST %CV	22.5	24.4	15.9	41.3											
DOSAGE FORM	REFERENCE %CV	31.3	31.1	23.3	42.7											
100 mg																
STRENGTH	ANOVA ERROR SS	124221685	136014944	420385	11.17											
0430 8C	ANOVA ERROR df	24	24	24	24											
TEST DRUG LOT NO.	NO. of SUBJECTS	26	26	26	26											
Single	NO. of TREATMENTS	2	2	2	2											
SINGLE/MULTIPLE DOSE STUDY	BALANCED? (YES/NO)	yes	yes	yes	yes											
Minocycline HCl																
COMPOUND	L.S. ESTIMATE															
1x100 mg	Std. ERROR ESTIMATE	630	660	36.7	.15											
DOSE ADMINISTERED	L.S. MEAN - TEST	13908	15425	830.7	1.88											
Minocin	L.S. MEAN - REFERENCE	12512	14102	725.4	2.038											
REFERENCE PRODUCT NAME	90% CI - LOWER BOUND	102	101	106	80											
Capsule	90% CI - UPPER BOUND	120	117	123	119											
REFERENCE DOSAGE FORM																
268-494																
REFERENCE LOT NO.																
Lederle																
REFERENCE PRODUCT SPONSOR																

approval
RECOMMENDATION
(APPROVE/DISAPPROVE, INCOMPLETE?)

REVIEWER

Minocycline Hydrochloride
100 mg Capsules
ANDA # 63-065
Reviewer: Man M. Kochhar
Wang # 5210f

-3 16 89

Danbury Pharmacal, Inc.
Danbury, Connecticut
Submission Date:
October 6, 1988

Review of Bioequivalence Study and Dissolution Data

Objective:

A two-way, single dose crossover study was performed to determine the bioequivalency of two minocycline hydrochloride formulations. Danbury's 100 mg capsules were compared to 100 mg Minocin^{R} (reference), marketed by Lederle Laboratories.

Introduction:

Minocycline hydrochloride is a semisynthetic derivative of tetracycline. The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Minocycline hydrochloride is a tetracycline with antibacterial activity comparable to other tetracyclines with activity against a wide range of gram-positive and gram-negative organisms.

Minocycline is well absorbed orally. Peak concentrations occur within 2-3 hours and in the range of mcg/ml with a single 200 mg dose. The serum half-life ranges from 15-23 hours.

About 11% of the dose is excreated unchanged in the urine and 20 to 34% in the feces. The drug is partly metabolized to inactive compounds in the liver.

Study Protocol:

The study was conducted by under the supervision of

The study employed 17 healthy male volunteers between 19 and 50 years of age whose weight did not deviate by more than ± 10% of the ideal for their height and age (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematologic or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug abuse and prior sensitivity to the drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, and urinalysis). Subjects were required to take no prescribed medications for at least 15 days and no OTC products (especially aspirin-containing products) for at least 7 days prior to the initial dosing and to refrain from consumption of alcoholic or caffeine-containing foods and beverages from 48 hours prior to dosing in each period and throughout the time samples were collected in each period.

The subjects were housed in the live-in facility from 12 hours before until 14 hours after drug administration. The subjects fasted for 10 hours prior to the first drug administration of phase 1. No meals were served within 5 hours of any dose. Water ad lib was allowed except within 2 hours of drug administration.

The product and dosage employed in this study were as follows:

A. Test: 2 x 100 mg minocycline capsule, lot # 00755C, with 240 ml of water.
B. Reference: 2 x 100 mg Lederle's Minocin^{R} (minocycline), lot # 168-494 with 240 ml water.

Fifteen (15) ml of venous blood were drawn in Vacutainers with no anticoagulant at : 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours. The serum was separated and promptly frozen for analysis.

Urine samples were collected during the following intervals: -1 to 0, 0-1, 1-2, 2-4, 4-6, 6-8, 8-12 and 12-24 hours. The volume and pH were measured and a 15 ml aliquot was saved for future assay.

Analytical Methodology:

Data Analysis:

All parameters were analyzed by Analysis of Variance and the F-test to determine statistically significant ($p < 0.05$) differences between the drug formulations. The statistical analysis was performed using SAS^{R} and PROC GLM for the analysis of varience. Evaluations of bioequivalency were based upon interproduct comparison of AUC, C_{MAX}, T_{MAX}, K_{el} and the timed serum minocycline concentrations.

In-Vivo Bioequivalency Results:

Seventeen subjects completed the study. The results of the study comparing the bioavailability of minocycline hydrochloride test and reference product are given in Table 1 and 2.

Table 1

Mean Serum Concentration of Minocycline Hydrochloride with CV% in Parenthesis (N=17)

Time (hours)	Danbury's Minocycline lot # 00755C mcg/ml	Lederle's Minocin lot # 168-494 mcg/ml
0.5	1.51 (74.45)	1.14 (84.23)
1	2.49 (48.18)	2.47 (48.16)
1.5	3.19 (39.32)	3.18 (37.42)
2	3.46 (23.97)	3.51 (26.38)
3	3.45 (23.91)	3.67 (25.03)
4	3.25 (25.71)	3.29 (25.75)
6	2.45 (24.46)	2.57 (20.87)
8	2.33 (31.97)	2.31 (19.84)
12	1.89 (28.13)	1.87 (20.25)
24	0.996 (22.23)	0.988 (18.55)
48	0.422 (25.16)	0.422 (34.53)
72	0.167 (37.71)	0.159 (39.78)

Table 2

A Summary of Pharmacokinetic Parameters for 17 Subjects (CV%)

Parameter	Danbury's Minocycline	Lederle's Minocin	% Diff	90% Confidence Interval
AUC_{0-72} (mcg.hr/ml)	71.6 (18.34)	71.5 (17.62)	0.14	95; 104
AUC_{Inf} (mcg.hr/ml)	76.0 (17.54)	75.6 (17.42)	0.52	96; 105
C_{MAX} (mcg/ml)	3.96 (25-35)	3.87 (22.02)	2.33	95; 110
T_{MAX} (hours)	2.68 (60.51)	2.56 (35.82)	4.69	
K_{el} (1/hr)	0.041 (16.07)	0.042 (16.37)	2.38	
$t_{1/2}$ (hours)	17.4 (17.82)	17.0 (17.06)	2.35	

The minocycline AUC_{0-72} of the Danbury product was 0.14% higher than the corresponding Lederle product. The AUC_{inf} was 0.53% higher than the reference. None of the differences was statistically significant at the 0.05 alpha level. The confidence intervals were well within the ± 20% limits set for defining product bioequivalence.

The differences between Danbury minocycline hydrochloride and Minocin C_{MAX} and T_{MAX} values were less than 5%. The 90% confidence interval for C_{MAX} was 95 to 110.

The minocycline hydrochloride/time profiles of the two products were virtually superimposable with less than 20% difference between the products being observed at each of the timed collection points.

No serious adverse events were experienced by any subject during the study.

On the basis of the in-vivo bioavailability data, it is determined that Danbury's Minocycline hydrochloride, 100 mg capsules and Lederle's Minocin[R], 100 mg capsules are bioequivalent.

Dissolution Test Results:

In-Vitro dissolution testing was conducted in apparatus 1 (paddle) at 50 rpm. Results are presented in Table 3. Both the test and reference products meet the dissolution specification of NLT % of the labeled amount of the drug dissolved from the capsule in 45 minutes.

The lot of test and reference product employed in the in-vitro dissolution tests were identical to those employed in the in-vivo bioequivalence study.

Comments:

1. The study was conducted in 17 normal male volunteers, comparing the serum concentration from Danbury's Minocycline HCl, 100 mg capsules to that of Minocin[R], 100 mg capsules. The minocycline hydrochloride AUC_{0-72}, AUC_{inf} and C_{MAX} of the Danbury's formulation were 0.14% higher, 0.53% higher and 2.33% higher than the corresponding Lederle's reference values. The differences were not statistically significant. These results indicate that the test drug is bioequivalent to the reference product.

2. The in-vivo bioequivalence study is acceptable. The firm should be informed accordingly.

3. The in-vitro dissolution testing conducted by the firm is acceptable. Both the test and reference products show greater than % of the labeled amount of minocycline hydrochloride dissolved in 45 minutes.

4. The lots of the test and reference product employed in the in-vitro dissolution test were identical to those employed in the in-vivo bioequivalence study.

Recommendations:

1. The bioequivalence study conducted by Danbury Pharmacal, Inc. on its minocycline hydrochloride, 100 mg capsules, lot # 00755C, comparing it to Minocin[R], 100 mg capsules, lot # 168-494, manufactured by Lederle has been found acceptable by the Division of Bioequivalence. The study demonstrates that Danbury's minocycline hydrochloride, 100 mg capsules are bioequivalent to reference product, Minocin[R], 100 mg capsules manufactured by Lederle Laboratories.

2. The Division of Bioequivalence recommends that the TEST PRODUCT BE CODED AB IN THE THERAPEUTIC EQUIVALENCE LIST.

3. The in-vitro test results were also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37°C using USP XXI apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than % of the labeled amount of the drug in the capsule is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in-vivo and in-vitro dissolution test and the application is approvable.

/S/

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/

MMKochhar/rlh/02-22-89/Wang #5210f

cc: ANDA # 63-065 original, HFD-230, HFD-200 (Hare), HFD-340 (Turner), HFD-22 (Hooton), HFD-258 (Mhatre, Kochhar), Drug File

Table 3

Results

Time in minutes	Test Product Lot # 00755C Mean % Dissolved	Range	(CV) %	Reference Product Lot # 328-186 Mean % Dissolved	Range	(CV) %
15	65.9		(20.5)	58.4		(15.6)
30	90.7		(5.4)	81.7		(8.2)
45	94.9		(3.4)	81.7		(6.7)
60	95.5		(5.4)	84.7		(8.4)
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

	Lot # _____			Lot # _____		
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
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